

# Relationship of Dietary Iodide and Drinking Water Disinfectants to Thyroid Function in Experimental Animals

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The importance of dietary iodide on the reported hypothyroid effect of drinking water disinfectants on thyroid function was investigated. Previous studies have also showed differences in the relative sensitivity of pigeons and rabbits to chlorinated water. Pigeons and rabbits were exposed for 3 months to diets containing high (950 ppb) or low (300 ppb) levels of iodide and to drinking water containing two levels of chlorine. Results showed that the high-iodide diet prevented the hypothyroid effect observed in pigeons given the low-iodide diet and chlorinated drinking water. Similar trends were observed in rabbits exposed to the same treatment; however, significant hypothyroid effects were not observed in this animal model.

The factor associated with the observed effect of dietary iodide on the chlorine-induced change in thyroid function is unknown, as is the relative sensitivity of rabbits and pigeons to the effect of chlorine. Several factors may explain the importance of dietary iodide and the relative sensitivity of these species. For example, the iodine formed by the known reaction of chlorine with iodide could result in a decrease in the plasma level of iodide because of the relative absorption rates of iodide and iodine in the intestinal tract, and the various types and concentrations of chloroorganics (metabolites) formed in the diet following the exposure of various dietary constituents to chlorine could affect the thyroid function. The former factor was investigated in the present studies. Results do not confirm a consistent, significant reduction in the plasma level of iodide in rabbits and pigeons exposed to chlorinated water and the low-iodide diet. The latter factor is being investigated.

## Introduction

Several investigators have observed hypothyroidism in experimental animals exposed to drinking water containing the disinfectant chlorine (pH 8.5), chlorine dioxide, or monochloramine (1, 2). The concentration of the disinfectant used in one study to produce the hypothyroid effect in pigeons (white Carneau) was within the range observed in some municipal drinking water supplies (2). The latter study (2) suggests that drinking water disinfectants may pose a human health problem. However, the hypothyroid effect reported in pigeons was not observed in rabbits exposed to these three drinking water disinfectants at similar concentrations. The factors associated with the relative thyroid sensitivity of these animal models to the disinfectants is presently unknown. The level of iodide in the diets fed to the pigeons and rabbits may explain these differences. For example, the level of iodide in the pigeon feed was

300 ppb, whereas iodide levels of 950 ppb were measured in the rabbit feed. It is well documented that chlorine will oxidize iodide to molecular iodine (3), which can react with organic matter and give rise to iodoorganic compounds (4). The formation of these compounds may reduce iodide in the intestinal tract and thereby reduce the intestinal absorption and plasma level of iodide. A decrease in the level of plasma iodide can promote hypothyroidism. Thus an increase in the dietary level of iodide may prevent the hypothyroid effect observed in pigeons exposed to relatively low levels of iodide.

To determine the importance of dietary iodide on thyroid function, rabbits and pigeons were exposed to the disinfectant chlorine and diets containing relatively high (950 ppb) and low (300 ppb) levels of iodide. At 1-month intervals for 3 months, the plasma levels of cholesterol, 3',5',3,5-tetraiodothyronine (T<sub>4</sub>), and free and bound iodine were measured. Cholesterol was determined in these studies because hypercholesterolemia is frequently observed in patients with hypothyroidism. Also, previous studies have shown increases in plasma cholesterol in pigeons receiving chlorinated drinking water.

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## Materials and Methods

### Exposure Studies

Male white Carneau pigeons and New Zealand white rabbits (3-month-old animals obtained from Palmetto Pigeon Farm, Sumter, SC, and Hazelton Rabbit Farm, Hazelton, PA) were housed in stainless-steel cages in an amber-lighted room during the experimental period. They were given, *ad libitum*, doubly deionized distilled water or drinking water containing 15 ppm chlorine (pH 6.5 or 8.5) and a diet (a single lot feed over the experimental period) containing two levels of iodide. These levels were adjusted by the manufacturer (Ziegler Bros., PA) so that feed contained 300 or 950 ppb iodide as confirmed by the investigators of this study.

The dietary calcium level was reduced from 0.9% to 0.35% because previous studies had shown dietary calcium to enhance the effect of the drinking water disinfectants on plasma cholesterol,  $T_4$  and  $T_3$ . The dietary levels of iodine and calcium were amended by altering the amounts of added potassium iodide and calcium carbonate. The chlorinated water was prepared as previously described (4,5) and the pH adjusted to 6.5 or 8.5 with hydrochloric acid (HCl) or sodium hydroxide (NaOH), respectively. The chlorinated drinking water was prepared and changed daily throughout the experimental period.

Pigeons and rabbits were exposed to the drinking water and diets for 3 months, during which blood samples (2 mL) were collected and the plasma was isolated monthly. Prior to the exposure, blood samples were taken and the plasma levels of cholesterol and  $T_4$  determined. During the experimental period, the plasma levels of cholesterol and  $T_4$  were determined at monthly intervals, and plasma iodine was measured after three months of exposure.

### Plasma Measurements

Plasma cholesterol was determined by the method of Allain et al. (6). All samples were measured in triplicate, and internal controls (provided by the Center of Disease Control, Atlanta, GA) were analyzed along with each sample. Total plasma  $T_4$  (free and bound) was measured by a radioimmunoassay using a coat-A-count kit provided by Diagnostic Products (Los Angeles, CA). Within assays, the coefficient of variation for  $T_4$  ranged from 4.7% to 9.8%.

### Iodine Studies

Iodine in the plasma and feed was determined by the iodide-catalyzed reduction of ceric ion ( $Ce^{4+}$ ) by arsenite ( $As^{3+}$ ) (7). To 0.5 mL of plasma was added 3 mL of distilled water, 0.5 mL of zinc sulfate ( $ZnSO_4$ ) (330 mM), and 0.5 mL of 0.5N NaOH. The sample was centrifuged, the aqueous layer was removed, and the precipitate was washed three times with deionized water. The aqueous layer and the three washes were combined, and free

iodine was determined. The precipitate was mixed with 0.5 mL of 4 N potassium hydroxide (KOH) and placed in a drying oven at 110°C for 6 hr. After drying, the precipitate was ashed in an incinerator at 620°C for 90 min. The ash was dissolved in 4 mL of water, and, after mixing, the samples were centrifuged and iodine determined in the aqueous layer by the decolorization of ceric ammonium sulfate by arsenite in acid solution. The iodine in the washed ash represents bound iodide. This method and the calculations used to determine free and bound iodine are similar to those previously reported by the American Official Analyst Committee (AOAC) (8, 9).

Iodide levels were determined in the rabbit and pigeon feed as described above. All determinations were done in triplicate for the various feeds. In experiments performed to determine the effect of chlorine (pH 6.5 and 8.5), chlorine dioxide, and monochloramine (2 and 15 ppm) on the release of bound iodide, a 1-g sample of feed was mixed with 10 mL of deionized water or water containing the individual disinfectants at the appropriate concentrations. The sample was incubated overnight, and the clear aqueous layer was removed following centrifugation. The residue was washed three times with the appropriate water, and 4 N KOH was added to the residue after the last wash. The residue was dried and ashed and bound iodine determined as described above. All experiments were performed in triplicate, and the methods of addition were used to determine iodine recovery in the residue. Recoveries in these studies were 97% to 106%.

### Statistical Analysis

Results were analyzed for statistical significance by Student's *t*-tests of the difference between means and of paired observations (10). The expressions  $p < 0.05$ ,  $p < 0.01$ , and  $p < 0.001$  were used to indicate significance at 5%, 1% and 0.1%, respectively.

## Results

Table 1 shows the ingredients used in the pigeon and rabbit diets, which were similar with the exception of the source for crude protein. Animals were exposed to the respective diets with relatively low (300 ppb) and high (950 ppb) levels of iodide and the various types of drinking water as shown in Table 2. The minimum daily requirement of iodide for pigeons and rabbits has been estimated as approximately 250 ppb (11). It is assumed, therefore, that the low-iodide diet will be adequate for maintaining normal thyroid function.

The significant changes shown in Tables 2 and 3 for plasma cholesterol,  $T_4$ , and iodine were determined by comparing within each treatment group the zero-time and 3-month values (i.e., plasma cholesterol and  $T_4$ ) or by comparing the controls and experimental groups at 3 months of exposure (i.e., plasma iodine). Significant statistical calculations were made within each treatment

Table 1. Dietary ingredients in rabbit and pigeon feed.<sup>a</sup>

Ingredient	Amount, %	
	Pigeon	Rabbit
Crude protein	20.82	17.2
Crude fat	3.55	2.4
Crude fiber	3.1	18.0
Ash	5.50	5.9
NEF	54.0	44.8
Amino acids	10.45	7.75
Bulk elements	2.37	3.74
Trace elements	0.0361	0.0467
Vitamins	0.177	0.192
Total	100	100

<sup>a</sup>These diets, the National Institutes of Health open formula diets, have been altered as follows: calcium reduced from 0.9% to 0.35%; and iodide reduced from 0.950 to 0.3 ppm. Crude protein is calculated from the addition of the following ingredients: in the pigeon diet, ground yellow corn, corn gluten meal, soybean meal, dehydrated alfalfa meal, and dried whey are added as a crude protein source; in the rabbit diet, alfalfa meal, ground oat hulls, soybean meal, ground barley, wheat middlings, wheat bran, and dried whey are added for protein.

group because of the variation at zero time for plasma cholesterol and T<sub>4</sub>.

Rabbit plasma cholesterol (Table 2) in the controls increased by 2 mg/dL when fed diet A (low iodide) and decreased by 10 mg/dL when fed diet B (high iodide). These differences, although not significant, changed in the direction that would have been predicted based on the dietary effect of iodide. In rabbits exposed to diet A and chlorinated water for 3 months, plasma cholesterol increased from the respective zero-time value by 18 mg/dL. When the experimental values at 90 days of exposure in group A were compared to those of the controls at the same exposure time, a mean increase of 14 mg/dL was observed. However, these mean changes in plasma cholesterol were not significant. In rabbits exposed to the chlorinated water and diet B, cholesterol levels increased by 2 mg/dL from the respective zero-

time value, whereas a decrease of 10 mg/dL was observed when compared to the controls.

The effects of chlorine on thyroid function in the rabbit are shown in Table 2. The plasma level of T<sub>4</sub> in rabbits decreased from the zero-time level in all groups. Significant decreases ( $p < 0.05$ ) were observed only when the zero-time value was compared to the 3-month values in the experimental groups given diet A and chlorine at pH 6.5. When the experimental 3-month value for diets A and B was compared to the controls at 3 months, significant differences were not observed. Free iodine levels in the plasma decreased in rabbits exposed to diet A and chlorinated water at pH 8.5. No significant changes in bound iodine in either dietary group were observed even though T<sub>4</sub> levels were decreased in animals given diet A and chlorinated water.

Plasma cholesterol in pigeons (Table 3) given diet A and chlorinated water for 3 months showed a mean increase of 42 mg/dL over controls at this same exposure period, with significant changes in plasma cholesterol over controls observed only in the group receiving diet A plus chlorinated water at pH 8.5. When the plasma cholesterol level at zero time was compared to the 3-month level in the groups given diet A and chlorinated water at pH 6.5 and 8.5, significant ( $p < .05$ ) increases of 84 mg/dL were observed only at pH 8.5. This 84 mg/dL increase is 40% greater than that observed in the group receiving the chlorinated water at pH 6.5. Similar observations were reported previously (2). No significant changes in pigeons given diet B and the chlorinated water were observed.

The plasma T<sub>4</sub> levels (Table 3) in the controls at three months were higher than those observed in the experimental groups exposed to diet A and chlorinated water. In these groups, significant changes (compared to the respective zero-time values) were observed in the group receiving chlorinated water at pH 8.5 and diet A. In pigeons fed diet B, plasma T<sub>4</sub> levels were increased from the respective zero-time value, although these changes

Table 2. Effect of chlorinated drinking water and dietary iodine on plasma cholesterol, T<sub>4</sub>, and iodine in rabbits exposed for 3 months.

Plasma level	Diet	Control (deionized water)		Chlorine (15 ppm, pH 6.5)		Chlorine (15 ppm, pH 8.5)	
		Zero time	3 months	Zero time	3 months	Zero time	3 months
Cholesterol, mg/dL	Low iodide	28.0 ± 4.5	30.0 ± 8.0	26.4 ± 6.0	44.0 ± 8.6	25.0 ± 4.9	43 ± 6.2
	high iodide	52 ± 10	42 ± 14	40 ± 7.8	41 ± 8.4	29 ± 5	31 ± 4
T <sub>4</sub> , µg/dL	low iodide	1.8 ± 0.28	1.38 ± 0.17	2.6 ± 0.19	1.57 ± 0.26*	2.9 ± 0.13	2.1 ± 0.10
	High iodide	2.2 ± 0.15	1.98 ± 0.11	2.9 ± 0.12	2.4 ± 0.26	2.0 ± 0.11	1.8 ± 0.14
Iodine, µg/dL							
Free	Low iodide	1.42 ± 0.76		1.54 ± 0.62		0.46 ± 0.09†	
	High iodide	2.47 ± 0.45		2.93 ± 0.93		1.93 ± 0.56	
Bound	Low iodide	4.75 ± 0.52		6.10 ± 1.1		5.22 ± 0.27	
	High iodide	4.16 ± 1.31		4.40 ± 0.93		5.13 ± 0.74	
Total	Low iodide	6.07		7.66		5.67	
	High iodide	6.63		7.33		7.06	

\* Mean ± SEM for four to five animals per experimental group.  $p < 0.05$  and  $p < 0.01$  were calculated by comparing within each treatment group the zero-time and 3-month values (i.e., plasma cholesterol and T<sub>4</sub>) or by comparing the controls and experimental groups at 3 months of exposure (i.e., plasma iodine).

\* $p < 0.05$ .

† $p < 0.01$ .

**Table 3. Effect of chlorinated drinking water and dietary iodine on plasma cholesterol, T<sub>4</sub>, and iodine in pigeons exposed for three months.<sup>a</sup>**

Plasma level	Diet	Control (deionized water)		Chlorine (15 ppm, pH 6.5)		Chlorine (15 ppm, pH 8.5)	
		Zero time	3 months	Zero time	3 months	Zero time	3 months
Cholesterol, mg/dL	Low iodide	250 ± 12	246 ± 14	244 ± 21	295 ± 10	197 ± 17	281* ± 19
	High iodide	283 ± 31	278 ± 27	312 ± 19	310 ± 27	262 ± 17	281 ± 18
T <sub>4</sub> , (μg/dL)	Low iodide	2.89 ± 0.15	2.60 ± 0.41	2.48 ± 0.23	1.80 ± 0.23	2.51 ± 0.34	1.30† ± 0.15
	High iodide	2.76 ± 0.38	2.90 ± 0.29	2.76 ± 0.90	2.80 ± 0.38	2.87 ± 0.18	3.34 ± 0.36
Iodine, μg/dL							
	Free						
	Low iodide	0.97 ± 0.18		1.29 ± 0.62		1.86 ± 0.60	
	High iodide	1.83 ± 0.13		2.05 ± 0.31		3.94 ± 0.83*	
	Bound						
	Low iodide	4.67 ± 0.88		3.04 ± 1.54		3.27 ± 0.33	
	High iodide	3.46 ± 0.38		5.06 ± 0.79		3.46 ± 0.29	
Total	Low iodide	5.59		6.35		5.13	
	High iodide	5.39		5.09		7.40	

<sup>a</sup> Mean ± SEM for four to five animals per experimental group.  $p < 0.05$  and  $p < 0.01$  were calculated by comparing within each treatment group the zero-time and 3-month values (i.e., plasma cholesterol and T<sub>4</sub>) or by comparing the controls and experimental groups at 3 months of exposure (i.e., plasma iodine).

\* $p < 0.05$ .

† $p < 0.01$ .

were not significant. The only significant change observed for plasma iodine was an increase in the level of free iodine in the group receiving diet B and chlorinated water at pH 8.5.

The results thus far suggest that dietary iodide in the pigeon may alter the effect of chlorine on the thyroid function. In an attempt to explain this observation, the effect of chlorine (pH 6.5 and 8.5) and two other commonly used disinfectants (chlorine dioxide and monochloramine) on the release of bound iodide from diet was investigated. It has been suggested that iodide is absorbed through the intestinal tract at twice the rate of iodine. Chlorine is known to react chemically with iodide, giving rise to iodine, and is also thought to react with iodoorganics, giving rise to a chloroorganic and iodine. The reaction of chlorine with free and bound iodide may increase the dietary level of iodine and thus reduce the relative absorption of iodide with a subsequent change in thyroid function. Results shown in Table 4 suggest that these disinfectants, when added to the diet, reduce the level of bound iodide. Significant changes in bound iodide were not observed when the relative level of iodide was high in both the pigeon and rabbit diets. The greatest change was observed in the pigeon diet at low and high iodide levels when chlorine (pH 8.5), chlorine dioxide, or monochloramine was added at a concentration of 15 ppm. In the high-iodide rabbit diet, the addition of 2 ppm resulted in higher levels of bound iodide.

## Discussion

The effect of dietary iodide and drinking water disinfectants on thyroid function of rabbits and pigeons was investigated. It was apparent that dietary iodide in the pigeon influenced the effect of chlorinated water on thyroid function. Pigeons given the low-iodide diet and chlorinated water exhibited significant changes in plasma cholesterol and T<sub>4</sub>. However, significant changes

**Table 4. Effects of drinking water disinfectants on bound iodine in diets of pigeons and rabbits.<sup>a</sup>**

Treatment group	Low iodide diet, μg/kg		High-iodide diet, μg/kg	
	Pigeons	Rabbits	Pigeons	Rabbits
Controls	146 ± 18	176 ± 20	218 ± 29	272 ± 30
Chlorine (pH 6.5)				
2 ppm	133 ± 15	141 ± 18	238 ± 40	327 ± 24
15 ppm	101 ± 8	107 ± 24	231 ± 28	243 ± 38
Chlorine (pH 8.5)				
2 ppm	131 ± 18	134 ± 19	197 ± 15	291 ± 27
15 ppm	92 ± 7*	110 ± 28	181 ± 17	240 ± 33
Chlorine dioxide				
2 ppm	149 ± 15	126 ± 10	202 ± 19	292 ± 35
15 ppm	91 ± 9*	82 ± 13†	185 ± 17	247 ± 17
Monochloramine				
2 ppm	110 ± 15	148 ± 22	195 ± 16	321 ± 39
15 ppm	64 ± 10*	119 ± 13	191 ± 19	325 ± 26

<sup>a</sup> Mean ± SEM of two experiments per diet and per concentration of disinfectant. The ingredients in the low- and high-iodide diets are shown in Table 1. The procedure for measuring bound iodine and the effect of these disinfectants on the release of bound iodine are discussed in the Materials and Methods section. The concentrations of total iodine in the low- and high-iodide diets were 305 ± 29 and 956 ± 100 and 288 ± 36 and 985 ± 93, for pigeons and rabbits, respectively.

\* $p < 0.05$ .

† $p < 0.01$ .

in these plasma constituents were not observed in pigeons fed the high-iodide diet and chlorinated water. In rabbits exposed to the low-iodide diet and chlorinated water, insignificant changes were observed for plasma cholesterol, T<sub>4</sub>, and bound iodine. However, we did observe that high dietary iodine in rabbits prevented the small changes observed in the low-iodide group exposed to the chlorinated water, which suggests that statistical significance may be achieved with a larger number of experimental animals.

The results of these studies suggest that chlorinated

water may induce hypothyroidism in pigeons as evidenced by significant changes in plasma  $T_4$  and cholesterol. The plasma concentration of cholesterol is significantly elevated in clinical hypothyroidism and generally bears a reciprocal relationship to the level of thyroid activity (12-14). However, the existence of similar reciprocal relationships in pigeons remains to be established. Nevertheless, we observed in previous (15, 16) and the present studies that a correlation exists between plasma cholesterol and thyroid activity. Furthermore, present studies suggest that dietary iodine may alter the effect of chlorine on both plasma cholesterol and  $T_4$ .

The relationship of chlorine to thyroid activity is not known. However, the fact that relatively high dietary levels of iodine prevented the significant effect of chlorine on plasma cholesterol and  $T_4$  suggests that this disinfectant may affect iodine metabolism when the dietary level of iodide is relatively low. It has been shown that chlorine reacts with iodide, giving rise to iodine, an active oxidizing species (17, 18). Iodine in the presence of organic matter would be expected to react and give rise to iodoorganics. Chlorine is also thought to react with iodoorganics, affecting the release of iodide and possibly the substitution of chlorine at the iodide-vacated site. A decrease in the level of dietary iodine could reduce the plasma level of iodide and thus the activity of the thyroid because iodide is absorbed through the intestinal tract at a rate greater than that of iodine. In an attempt to determine the validity of this assumption, the effect of drinking water disinfectants on the release of bound iodide in the rabbit and pigeon diet was investigated. Results showed that these disinfectants reduce the level of bound iodide in the diet, the magnitude depending on the concentration of the disinfectant and the dietary level of iodide. For example, a significant decrease in the level of bound iodide was observed when the concentration of the disinfectant was increased from 2 to 15 ppm. However, this effect was only observed when the low-iodide diet was used, which suggests that the dietary level of iodide may influence the effect of these disinfectants on the release of bound iodide in the diet.

These *in vitro* studies suggest that these disinfectants reduce the level of bound iodide in the diet. If these effects occur *in vivo*, the dietary levels of iodide may be reduced to a level that significantly affects plasma iodide. Significant decreases in plasma iodide (i.e., both free and bound) in pigeons were not observed following the exposure to the chlorinated water. Thus it appears that although these disinfectants may affect the dietary level of bound iodide, they do not seem to significantly alter plasma iodide levels.

Other factors that may explain the observed hypothyroid effect of these disinfectants include hypothyroid induction by chloroorganics. Several investigators have shown that chloroorganics are formed when various feeds are mixed with chlorine (19, 20). Formation of these compounds may vary with the dietary constituents. Thus, differences in formation rates and species

of chloroorganic compounds in the intestinal tract may explain the difference in sensitivity of rabbits and pigeons to chlorinated water. Studies are in progress to determine if chloroorganics are formed in diets mixed with chlorine and if the formed chloroorganics affect the thyroid function.

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